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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/415,795	10/08/1999	PENGBO ZHOU	HMV-043.01	5319

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/415,795	ZHOU ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13 and 16-56* is/are pending in the application.

4a) Of the above claim(s) *12,13,16-35 and 50-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *36-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *19* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 3, 2002 has been entered.

The preliminary amendment filed September 3, 2002 canceling claims 1-4, 6-11, 14 and 15 and adding claims 36-54 has been entered.

However, there were two claims 44 and two claims 45.

In accordance with 37 CFR § 1.126, the claims have been renumbered 36-56. The new numbers have been used thenceforth.

Claims 12, 13 and 16-56 are pending. Claims 12, 13 and 16-35 are withdrawn (see Office action mailed August 6, 2001). Claims 36-56 are under consideration.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 36-49, drawn to a method for targeting degradation of a polypeptide using an F-box polypeptide, classified in class 435, subclass 68.1.

II. Claims 50-53, drawn to a DNA encoding an F-box fusion protein, classified in class 536, subclass 23.2.

III. Claims 54-56, drawn to an F-box fusion protein, classified in class 435, subclass 183.

The inventions are distinct, each from the other because of the following reasons:

Inventions III and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case an F-box polypeptide fusion can be used for the production of an antibody and in a screening assay to determine the target, for example.

Inventions II and III are patentably distinct because a DNA and an F-box polypeptide are different compounds each with its own chemical structure and function, and they have different utilities. A DNA molecule of invention II can be used for targeting the polypeptides inside the cell and for the large scale production of a

polypeptide of invention III. A polypeptide of invention III can be obtained by a materially different method such as by chemical synthesis.

Therefore, newly submitted claims 50-56 are directed to inventions that are independent or distinct from the invention originally claimed for the reasons indicated above. Furthermore, claims 36-49 are generic to a plurality of disclosed patentably distinct species of SEQ ID NOs: 2, 4, 6, 8, 10 and 12. Applicants elected the species of SEQ ID NO: 4 in Paper No. 13 filed May 29, 2001 (Office action mailed August 6, 2001).

RCE provides continued examination of an application. Claims 36-49 are considered as corresponding to the previously examined claims.

Accordingly, claims 50-56 are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 41-45 have only been examined with respect to the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-40 and 45-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of hybrid polypeptides comprising F-box polypeptide and a target interaction domain.

"F-box polypeptides" encompass proteins of diverse structures and, in many cases, unknown function.

The specification does not contain any disclosure of the structure and function of all hybrid polypetides comprising F-box polypeptide and a target interaction domain. The genus of hybrid polypetides that comprise these above molecules is a large variable genus comprising many different proteins. Therefore, many structurally and functionally unrelated F-box and hybrid polypeptides are encompassed within the scope of these claims. The specification discloses only a three species of the claimed genus, hybrid of Cdc4 with LTP and E7N and a hybrid of βTrCP fused with E7N. In these cases, the known interaction domain was fused to a known component of a ubiquitin pathway and used for degrading a respective target. Both Cdc4 and βTrCP contain in addition to F-box a WD domain. There is a showing that both F-box and the WD domain is essential for degrading function (page 133). There is no showing that F-box is sufficient to impart the requisite function. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than being a *F-box* polypeptide and fails to provide any

structure:function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for degradation of target polypeptides using hybrid polypeptides comprising Cdc4/βTrCP and known target polypeptide interaction domain, such as LTP and E7N, in yeast and human cells, respectively, does not reasonably provide enablement for a method of use of a hybrid comprising any F-box polypeptide for which target polypeptide and ubiquitin proteolysis pathway is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claims 36-49 are drawn to a method of use of any hybrid polypeptide comprising any F-box polypeptide and a target polypeptide interaction domain in any host cell. This amounts to any hybrid polypeptide comprising peptide structures both naturally-occurring and man-made. "F-box polypeptides" encompass proteins of diverse structures and, in many cases, unknown function.

The art teaches that "F-box proteins directly contact ubiquitination substrates and can display selectivity in recognition of potential targets for ubiquitination, as would be expected of E3 proteins" (Skowyra et al., form PTO-1449 mailed November 14, 2000, reference AF, page 215, 2nd column). The art teaches the composition of *Saccharomyces cerevisiae* SCF ubiquitin ligase complex (ibid, for example).

However, ubiquitin proteolysis pathways are not yet elucidated in most settings. Without knowing the target interacting domain and its target as well as corresponding F-box protein, it is impossible to construct a requisite hybrid. Without knowing the pathway it is impossible to reconstitute it *in vitro*.

The specification teaches a method of use of a hybrid of Cdc4 with LTP and E7N for degrading pRB when both the hybrid and pRB were expressed in *S. cerevisiae* Y81 cells (page 135). The specification further teaches a method of use of a hybrid of a human analog of Cdc4, βTrCP, fused with E7N for degrading the endogenous protein, p107, that is human pRB analog, when expressed in human C33A cells (pages 138-139, Figure 11, page 140). Therefore, the specification teaches a method of use of a F-box polypeptide, Cdc4, and its human analog, βTrCP, fused to a known target polypeptide interaction domain, for degrading of a known target polypeptide *in vivo* in isolated yeast and human cells, respectively.

The specification does not support the broad scope of the claims because of the following.

Despite knowledge in the art to produce hybrid proteins, the specification fails to provide guidance as to the composition and structure and function of components of other ubiquitin ligases that can be used in the claimed method other than Cdc4 and its human homolog. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. The specification teaches the use of Cdc4/βTrCP based hybrids in a host cell naturally containing other components of a ubiquitin ligase complex. The hybrid is cell specific, i.e., Cdc4 is used in yeast cells and βTrCP is used in human cells. It is unknown whether the method can be used in a bacterial cell, for example. The specification does not teach how to use a

hybrid comprising E7 and LTP and a second component other than Cdc4 in cells containing no pRB or p107.

Therefore, one of ordinary skill in the art would require guidance, in order to degrade any target polypeptide by using a hybrid comprising any F-box polypeptide in any cell other than a hybrid based on Cdc4 and βTrCP and known target polypeptide interaction domain in yeast and human host cell, respectively, in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim 44 is further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hybrid protein comprising F-box polypeptide of SEQ ID NO : 4, does not reasonably provide enablement for a hybrid protein comprising F-box polypeptide having 70% homology to SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 44 is so broad as to encompass a F-box polypeptide with 70% homology to SEQ ID NO: 4. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of F-box polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which

changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of a single F-box polypeptide having the amino acid sequence of SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claim which encompasses any F-box polypeptide with 70% homology to Cdc4 of SEQ ID NO: 4 because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting F-box activity; (B) the general tolerance of F-box polypeptide to modification and extent of such tolerance; (C) a rational and predictable

scheme for modifying any F-box polypeptide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any F-box polypeptide with 70% homology to SEQ ID NO : 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of F-box polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites "F-box" polypeptide. There is no clear definition of this term either in the art or in the specification. This renders the metes and bounds of the claim unascertainable. Claims 37-49 are rejected as dependent from claim 36.

Claim 36 is confusing as drawn to "a method for degrading a target polypeptide" while, in fact, reciting a method for targeting. Further, claim 36 is incomplete as omitting essential steps, such omission amounting to a gap between the steps. The omitted steps appear to be steps recited in claims 37 and 38.

Claims 37 and 38 are confusing because they recite steps that should precede the step of "degrading the target polypeptide" recited in claim 36 from which claims 37 ands 38 depend.

Claim 37 recites "SCF". It is unclear which molecules other than SCF complexes of *S. cerevisiae* are encompassed by the claim.

Claim 41 recites "beta TrCPp". It is unclear which molecules other than SEQ ID NO:4 are encompassed by the claim.

Claim 45 recites "stringent conditions". Because stringent conditions can mean different conditions, it is impossible to determine which molecules are included in the scope of the claim.

Claims 46 and 47 are unclear for reciting "in vitro" and "in vivo". Isolated cells can be considered both "in vitro" and "in vivo". On other hand, "in vivo" may be construed as a live organism. For the purposes of examination, the examiner construed

"in vivo" as limited to isolated cells in agreement with Applicants reference on page 142. This appears to be also in agreement with the meaning of "in vitro" and "in vivo" accepted in the pertinent art (for example, Skowyra et al., *supra*, Figure 3).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-39, 45, 46, 48 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheffner et al.

Scheffner et al. (form PTO-1449 mailed January 28, 2002 reference BF) teach degradation of the retinoblastoma protein by human papilloma virus type 16 (HPV-16) E7-E6 fusion proteins *in vitro*.

Scheffner et al. teach that HPV-16 E7 contains the binding domain for the retinoblastoma gene product pRB and p107 (page 2425, 2nd column).

Absent clear definition of "F-box polypeptide", E6 is construed as F-box polypeptide.

Claim 45 is included in the rejection because a DNA encoding E6 can hybridize to SEQ ID NO: 4 under some undefined conditions.

Therefore, Scheffner et al. anticipate claims 36-39, 45, 46, 48 and 49.

Response to Arguments

Applicant's arguments filed September 3, 2002 have been fully considered but they are not persuasive.

Applicants argue that F-box structures can be found on NCBI website (page 5, 1st paragraph). Regardless of whether it is possible to obtain the needed information on the website, the essential material such as F-box polypeptide must be defined in the specification.

Applicants argue that "there is ample support for making and using the F-box methods and compositions specifically claimed ..." (page 5, 2nd paragraph). This is not agreed with for the reasons given in the rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner